REMARKS

Status Summary

Claims 14-32 are pending in the subject application.

Claims 14-28 are currently canceled.

Claims 29-32 are pending and have been examined.

Favorable reconsideration is respectfully requested in view of the Amendments and Remarks.

Rejection of Claims 29-31 Under 35 U.S.C. § 103(a)

Claims 29-31 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Engle in view of Nielsen. According to the Patent Office:

> Engle teach immunizing CD19 transgenic mice overexpressing CD19 with an antigen. They teach that hCD19 transgenic mice had an overall increase in serum immunoglobulin levels. They go on to teach that overexpression of CD19 appears to render B cells more susceptible to differentiation induction. The data in table 2 show that the levels of isotype IgG2a and IgG2b antibodies are particularly higher in the hCD19 transgenic mice compared to wild type controls.

Official Action at pages 3-4.

After careful consideration of the rejection and the Patent Office's bases for the rejection, applicant respectfully traverses the rejection and submits the following.

Initially, applicant respectfully submits that in order to establish a prima facie case of obviousness, three basic criteria must be met. According to the Manual of Patent Examining Procedure (hereinafter the "MPEP"), § 2142:

> First, there must be some suggestion or motivation...to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) (emphasis added).

Furthermore, even when the combination of references teaches every element of the claimed invention, when a motivation to combine references is not found, a rejection

based on a prima facie case of obviousness is improper. In re Rouffet, 149 F.3d 1350, 47 USPQ2d 1453 (Fed. Cir. 1998). Additionally, "the level of skill in the art cannot be relied upon to provide the suggestion to combine references". MPEP § 2143.01, citing Al-Site Corp. v. VSI Int'l Inc., 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).

And finally, in Hodosh v. Block Drug Co., 786 F.2d 1136 (Fed. Cir. 1986), the U.S. Court of Appeals for the Federal Circuit set forth what is described as the "tenets of patent law that must be adhered to when applying §103", Id. at 1143, n.5. Those tenets set out in Hodosh are:

a) the claimed invention must be considered as a whole;

b) the references must be considered as a whole and suggest the desirability and thus obviousness of making the combination;

c) the references must be reviewed without benefit of hindsight vision afforded by the claimed invention; and

d) "ought to be tried" is not the standard with which obviousness is determined.

The Patent Office has asserted that Engle teaches immunizing CD19 transgenic mice overexpressing CD19 with an antigen, which resulted in an overall increase in serum immunoglobulin levels, particularly of the IgG2a and IgG2b isotypes. Engle is also asserted to teach that overexpression of CD19 appears to render B cells more susceptible to differentiation induction. However, the Patent Office concedes that Engle does not teach the production of monoclonal antibodies recited in steps (b) through (e) of claim 29 or specific affinity constants for the monoclonal antibodies produced. According to the Patent Office, this defect is cured by Nielsen. Nielsen is asserted to teach a method of making monoclonal antibodies via hybridoma formation similar to that claimed in steps (b) through (e) of claim 29, which can be used to obtain antibodies having an affinity constant greater than 1×10^5 L/mol.

Applicant respectfully submits, however, that even assuming arguendo that the Patent Office's assertions regarding the teachings of Engle and Nielsen are accurate, the Patent Office has not met its burden under 35 U.S.C. § 103(a) of presenting a prima facie case of obviousness because the Patent Office has not presented evidence that the references provide the skilled artisan with the motivation to combine the teachings

of the references to produced the claimed invention. In a previous Official Action, the Patent Office asserted that "the ordinary skilled artisan would have been motivated to modify the claimed invention because CD19TG mice could produce higher levels of antibodies, particularly when the desired isotypes of the antibodies are IgG2a, 2b, and IgM". Official Action dated February 13, 2003, at page 4. Applicant respectfully traverses this assertion, and as discussed in more detail hereinbelow, when the Engle reference is taken as a whole, one of ordinary skill in the art would not have been motivated to use CD19 transgenic mice for the production of monoclonal antibodies.

The Patent Office contends that the fact that CD19 transgenic mice had an overall increase in serum immunoglobulin levels provides the necessary motivation for using these mice to create monoclonal antibodies. However, further review of Engle reveals that when taken as a whole, this reference teaches that CD19 transgenic mice exhibit certain phenotypes that would dissuade one of ordinary skill in the art from using these mice as sources of antibody-producing cells for the production of hybridomas. For example, Engle teaches that the development of immature and mature B cells in the bone marrow of CD19 transgenic mice is severely impaired. See Engle at page 40. Furthermore, Engle teaches that in CD19 transgenic mice, immature B cells (IgM^+ $B220^{lo}$) were significantly reduced in the bone marrow, as were B cell numbers in the blood (95% decrease), spleen (82% decrease), and peritoneum (70% decrease). Applicant respectfully submits that given the abnormal B cell development observed in CD19 transgenic mice, particularly the lower B cell numbers in the spleen, one of ordinary skill in the art would not have been motivated to produce hybridomas using antibody-producing cells from CD19 transgenic mice.

Applicant further submits that the skilled artisan would not be motivated to use CD19 transgenic mice based on the Engle reference for another reason. Engle teaches that CD19 is involved in transmembrane signaling related to negative selection and clonal deletion of immature B cells in the bone marrow. According to Engle:

> The finding that overexpression of CD19 results in increased sensitivity to transmembrane signals in combination with the finding that overexpression of CD19 results in clonal elimination of B cells in the bone marrow suggests that CD19 regulates antigen-dependent negative selection of immature B cells during maturation in the bone marrow. Since impaired B cell development in hCD19TG mice is directly correlated with

> the number of cell surface hCD19 molecules expressed...increased receptor number may translate into the overproduction of intracellular signals, which exceeds the signaling threshold and results in down-regulation of immature B cell development. Since many preimmune B cells produce self-reactive antibodies...lowering the surface immunoglobulin signaling threshold for negative selection by overexpressing CD19 may explain the severe deficiency of B cells in hCD19TG mice...Thus, overexpression of CD19 may augment transmembrane signals generated through low affinity antigen receptors, thereby leading to increased clonal deletion of immature B cells in the bone marrow.

See Engle at page 47. As described in more detail therein, overexpression of CD19 leads to increased sensitivity to transmembrane signaling concomitant with increased antigen-dependent negative selection of immature B cells.

Increased clonal deletion and/or negative selection would be expected to result in a decrease in both the antigen-binding affinities and antigen-binding repertoire of the antibody-producing cells (and hence the antibodies produced by these cells) present in CD19 transgenic mice under conditions of augmented transmembrane signaling for at least two reasons. First, high affinity antibodies are more likely to be clonally deleted; and second, increased transmembrane signaling driven by CD19 overexpression would lead to the clonal deletion of antibody-producing cells that would not have been deleted in the absence of CD19 overexpression. Increased clonal deletion would result in a reduction in the numbers of B cells exiting the bone marrow (Engle specifically teaches that B cell numbers in the CD19 transgenic mice were drastically reduced both in tissues and in the blood). Therefore, the antigen-binding repertoire of CD19 transgenic mice would be expected to be reduced as compared to that seen in a wild-type mouse. As a result, applicant respectfully submits that one of ordinary skill in the art would expect the hybridomas produced using CD19 transgenic antibody-producing cells to produce a limited repertoire of low affinity antibodies, a fact that would strongly discourage the skilled artisan from employing these mice as sources of antibody-producing cells for the production of hybridomas. Given the time and expense required to produce monoclonal antibodies, applicant respectfully submits that one of skill would not begin this process if the likely result would be the production of low affinity monoclonal antibodies with a limited antigen-binding repertoire.

Accordingly, applicant respectfully submits that the skilled artisan would understand Engle to teach that the CD19 transgenic mice are characterized by significant defects in B cell development and maturation, and that these defects would have a drastically negative impact on the usefulness of these mice in the production of monoclonal antibodies. As such, applicant respectfully submits that the motivation to use CD19 transgenic mice for producing monoclonal antibodies cannot be found in Engle, and further that Engle actually teaches away from making monoclonal antibodies from CD19 transgenic mice.

Applicant further submits that it is only in the specification of the instant application that the antibody response in CD19 transgenic mice is shown to be unexpectedly diverse. Thus, applicant respectfully submits that the only motivation to create monoclonal antibodies using CD19 transgenic mice is found within the instant specification. According to the Court of Appeals for the Federal Circuit in Hodosh (cited hereinabove), however, the references cannot be viewed with this type of hindsight vision. Additionally, the specification of the instant application cannot be used to provide the motivation to combine the asserted references as per In re Vaeck.

Summarily, applicant respectfully submits that Engle does not provide the necessary motivation required to combine the cited references, and in fact teaches away from using CD19 transgenic mice to produce monoclonal antibodies. In the absence of this motivation, applicant respectfully submits that the Patent Office has not met its burden in establishing a prima facie case of obviousness of claims 29-31 over Engle in view of Nielsen.

In view of the arguments presented herein above, applicant respectfully submits that the subject matter encompassed by claim 29 of the instant application has been patentably distinguished from the teachings of Engle in view of Nielsen. Claims 30 and 31 depend from claim 29, and thus include these distinguishing elements. Accordingly, applicant respectfully requests that the rejection of claims 29-31 under 35 U.S.C. § 103(a) based upon these references be withdrawn, and that the claims be allowed at this time.

Allowed Claim

The Patent Office has indicated that claim 32 is allowable. Applicant would like to thank Examiner Li for her consideration of claim 32.

CONCLUSIONS

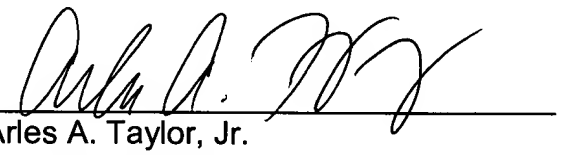
In light of the above remarks, applicant submits that the subject patent application is in condition for allowance and such allowance is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to place the application in condition for allowance.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any deficiencies of payment or credit any overpayments associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,
JENKINS, WILSON & TAYLOR, P.A.

Date: 02/06/2004 By: 

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